Clinical case
Do published ADA studies support the ADA-EASD position statement for the management of hyperglycaemia in type 2 diabetics?

Les études publiées à l’ADA confortent-elles la prise de position ADA-EASD pour la prise en charge de l’hyperglycémie chez les diabétiques de type 2 ?

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Abstract
The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a position statement in 2012 on the management of hyperglycaemia in patients with type 2 diabetes. The Société Francophone du Diabète (SFD) adopted it while awaiting future French recommendations. This new care approach individualises the therapeutic choices and objectives for each patient based on their characteristics, through emphasis on the need for mutual cooperation with the patient in decision-making. Glycaemic management should naturally be considered in the context of overall cardiovascular risk reduction, which should remain the primary objective of treatment. The cornerstone of this treatment is based on lifestyle modifications, with the addition of metformin monotherapy if the desired glycaemic control is not attained. There are multiple second- and third-line treatment possibilities, and insulin therapy is an option that can be considered early in the bitherapy stage. On the whole, large published studies at the ADA conference in Philadelphia in June 2012, which are the subject of this article, support this patient-centred position statement.
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Résumé
L’American Diabetes Association (ADA) et l’European Association for the Study of Diabetes (EASD) ont publié en 2012 une prise de position sur la prise en charge de l’hyperglycémie chez le patient diabétique de type 2. La Société francophone du diabète (SFD) l’a adoptée dans l’attente des futures recommandations françaises. Cette nouvelle approche de soin individualise les choix thérapeutiques et les objectifs pour chaque patient en fonction de ses caractéristiques en insistant sur la nécessité que les décisions soient prises en concertation avec lui. La prise en charge de la glycémie doit naturellement s’inscrire dans la perspective d’une réduction globale du risque cardiovasculaire qui doit rester l’objectif principal du traitement. La pierre angulaire de ce traitement repose sur les modifications du mode de vie auxquelles s’ajoute la monothérapie par metformine si l’équilibre glycaémique souhaité n’est pas atteint. Les possibilités de traitements de seconde et de troisième lignes sont multiples et l’insulinotherapie est une option envisageable précocement au stade de la bithérapie. Dans l’ensemble, les grandes études publiées au congrès de l’ADA à Philadelphie en juin 2012, qui font l’objet de cet article, confortent cette prise de position centrée sur le patient.
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1. Introduction
The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a position statement in 2012 on the management of hyperglycaemia in patients with type 2 diabetes [1,2]. The Société Francophone du Diabète (SFD) in turn adopted it, translated it and made it public while awaiting the French recommendations, which are soon to be published. This text is available on the SFD website (www.sfdiabete.org).

Contrary to previous algorithms that proposed therapeutic reinforcement based on the glycated haemoglobin value (HbA1c), this new care approach individualises the therapeutic options offered to patients based on their characteristics and mutually agreed objectives.

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The purpose of this article is to analyse whether the results of recently published studies from the ADA conference in Philadelphia in June 2012 are consistent with this new approach.

2. Glycaemic objectives

The HbA1c target chosen for the majority of patients in order to reduce microvascular disease is below 7%. In certain select patients (recent diabetes, long life expectancy, no associated cardiovascular disease), a stricter HbA1c target between 6% and 6.5% is required, provided that this objective can be reached without hypoglycaemia or any other undesirable treatment effect. Conversely, in patients with multiple complications, with history of severe hypoglycaemia, or reduced life expectancy, an HbA1c objective of 7.5% to 8% and even slightly higher is acceptable.

There are several factors that can help clinicians determine the HbA1c objective for a given patient: his/her motivation, the risk of hypoglycaemia and other undesirable effects, duration of diabetes, life expectancy, comorbidities, cardiovascular complications and the patient’s resources. Diabetes management in elderly patients is difficult. The characteristics of this population are not comparable to those of younger patients due to the associated comorbidities and cardiovascular risk factors. In the GERODIAB observational study, 987 autonomous type 2 diabetic patients over the age of 70 years were included: the mean age was 77 years. The mean duration of diabetes was 18 years and the mean body mass index (BMI) was 30 kg/m². Nearly 90% of patients presented with hypertension and 85% with dyslipidaemia [3]. The mean HbA1c was 7.5%. One-third of patients had presented with hypoglycaemia in the 6 months prior to inclusion. Of the complications, 26% had retinopathy, 37.2% had renal failure, 31.2% had coronary insufficiency and 15.8% had cerebrovascular involvement. An alteration in cognition upon admission was seen in 28.8% of patients, and 12.4% had protein-energy malnutrition.

The ADA-EASD position statement proposes that the therapeutic objectives take into account the distinctive characteristics of this population and the particular risks of each patient. The evaluation of the link between glycaemic control and mortality-morbidity at 5 years in the GERODIAB study certainly provided some answers for better management of these patients.

3. Choice and organisation of treatments

The ADA-EASD position statement also provides valuable indications for therapeutic choices, while leaving treatment choice to the discretion of clinicians, except in the initial phase, which is widely agreed upon.

3.1. Lifestyle modifications continue to be key

The first intervention naturally concerns dietary and physical activity modifications. The implementation of validated therapeutic educational programmes is essential for all patients. This initial therapeutic strategy applies to all diabetics and may serve to motivate them further, provided the therapeutic objectives are not too remote (HbA1c < 7.5%).

The Diabetes Prevention Program Outcomes (DPPOS) study, which was presented at the ADA conference, addressed lifestyle dietary and exercise management of type 2 diabetes [4]. It followed on from the Diabetes Prevention Program (DPP) study, published in 2002, which compared the efficacy of two preventive strategies on the occurrence of diabetes in prediabetic patients. These strategies included intensification of lifestyle dietary and exercise measures compared to treatment with metformin and with placebo [5]. The incidence of diabetes was lower at 3 years in the groups that implemented intensification of lifestyle interventions and that were treated with metformin (4.8 and 7.8%, respectively, versus 11% in the placebo group).

The DPPOS study focused on the 10-year follow-up of these three groups by comparing the patients who had returned to normal glucose regulation at least once over the 3 years of the intervention phase and those who remained prediabetic. Of the patients that had a return to normal glucose regulation during the DPP study, 56% were not diabetic at the subsequent follow-up, irrespective of the initial randomisation group. These results demonstrate the benefits of early lifestyle intervention at the prediabetic stage.

3.2. Monotherapy based on metformin

If lifestyle intervention is unsuccessful, metformin is the first-line drug for type 2 diabetes. To avoid any delay in achieving normal blood glucose levels, intensification can be anticipated if lifestyle modifications prove inadequate, as with monotherapy later on. Metformin acts mainly by reducing hepatic glucose production. It is an essential step in the therapeutic plan if there is no contraindication or intolerance.

Metformin nevertheless has a poor reputation, and as a result there is a certain reluctance towards its use due to exaggerated fears when lactic acidosis occurs. This complication is indeed serious, with a mortality of 30% to 50%, but fortunately it remains very rare provided that minimum precautions are taken when metformin is prescribed. In a retrospective study of 197 patients presenting with lactic acidosis, only 10 patients were taking metformin [6]. Six of them had previously had vomiting and/or diarrhoea, leading to acute renal failure, and three patients had chronic renal failure. The pH was significantly lower in patients with lactic acidosis who took metformin (6.78 versus 7.20 in lactic acidosis from other causes), and blood lactate levels were significantly higher (18.7 mmol/L versus 11.2 mmol/L). Mortality in patients taking metformin was lower when there was no other aetiology explaining the acidosis (50% versus 74%). It remains controversial however whether metformin accumulation is the only factor that triggers lactic acidosis [7]. Caution should therefore be used with regard to the indication for metformin treatment in patients with several risks, renal failure in particular, and special attention should be given to those unable to react adequately by discontinuing this treatment if an intercurrent event occurs.

The current joint recommendations of the Société de Néphrologie and the SFD advise the use of metformin at
normal doses in patients with a glomerular filtration rate over 60 mL/min, a decrease to half the dose in patients with a clearance between 60 and 30 mL/min and discontinuation of the treatment when below 30 mL/min [8].

### 3.3. If metformin fails, there are many treatment options

In the event of metformin monotherapy failure, there are multiple possibilities for additional treatments, thus a patient-centred care approach becomes all the more relevant [9]:

- treatment with sulfonylureas or glinides, which stimulate insulin secretion, may be considered in normal weight patients who have a high HbA1c and no major risk of hypoglycaemia. This therapy has actually been the only one available for decades, providing glycaemic control for a considerable number of patients. The benefit of glinides, with their short half-life, is that they can be used in patients with renal failure (clearance up to 10 ml/min). They are, in fact, the treatment of choice in fragile patients, since they cause less severe hypoglycaemia than the sulfonylureas [10];
- treatment with pioglitazone, which is no longer available in France, could be preferentially indicated in subjects presenting with insulin resistance markers (hepatic steatosis, increased waist circumference);
- treatment with a dipeptidyl peptidase-4 (DPP-4) inhibitor may be considered in subjects at risk for hypoglycaemia. The EASIE study, presented at the ADA conference, compared treatment with glargine to that of sitagliptin in type 2 diabetic patients who were uncontrolled with metformin (HbA1c >7%) [11]. It was a 6-month open-label study without placebo group in 732 patients. The mean age was 53 years, BMI 31 kg/m², HbA1c 8.5% and fasting glycaemia 9 mmol/L. The glargine group showed a significant reduction in HbA1c (6.8% versus 7.4% with sitagliptin), although with weight gain of 0.44 kg versus weight loss of 1.08 kg with sitagliptin, and more frequent hypoglycaemia (46% versus 13% with sitagliptin). The introduction of basal insulin at the bitherapy stage is therefore a possible strategy. For clinicians however, both of these treatments would probably not be used in the same types of patients. The DPP-4 inhibitors could be preferentially prescribed in fragile diabetics with a high risk of hypoglycaemia and with an HbA1c closer to the objectives;
- treatment with an injectable GLP-1 analogue may be indicated at this stage of metformin failure, particularly in obese subjects and especially if there is a risk of hypoglycaemia. The Liraglutide Effect and Action in Diabetes (LEAD) 2 study showed similar efficacy in HbA1c improvement with liraglutide 1.2 and 1.8 mg compared with glimepiride, all in combination with metformin [12]. Hypoglycaemia occurred significantly less frequently in the liraglutide group, with a weight loss of 2.5 kg versus a 1 kg weight gain with glimepiride. One study of 658 patients who were uncontrolled with metformin and had a baseline HbA1c of 8.5% compared the efficacy of sitagliptin and liraglutide [13]. The addition of liraglutide 1.2 and 1.8 mg significantly improved the HbA1c (1.50% reduction of HbA1c with liraglutide 1.8 mg and 1.24% with liraglutide 1.2 mg versus 0.90% with sitagliptin);
- finally, basal insulin therapy may be introduced in the beginning with significantly uncontrolled glycaemia including signs of insulinopaenia or when oral antidiabetic drugs are contraindicated. The ORIGIN study, which was presented at the ADA conference, had the aim of evaluating the effect of basal insulin (glargine) on cardiovascular risk [14]. A population of 12,537 prediabetic or recently diagnosed diabetic patients with high cardiovascular risk were included. The study was conducted over 6.2 years. Standard management was compared to the use of insulin therapy with glargine. There was no significant difference demonstrated with regard to death from cardiovascular origin, non-fatal myocardial infarction, non-fatal cerebrovascular accident or microvascular events. Patients from the glargine group had significantly more severe hypoglycaemia and weight gain (1.6 kg versus 0.5 kg in the standard group). This study was valuable as it proved the neutral effect of glargine on the incidence of and death from cancer. These results therefore demonstrate the feasibility and safety of early insulin therapy at the prediabetic stage or in recently diagnosed diabetics.

### 3.4. When bitherapy fails, many possibilities exist

If bitherapy failure occurs, a third drug other than insulin may be added to reach the set glycaemic objectives. A drug with a complementary mechanism of action is preferable, based on the patient’s characteristics. At this stage however, it is common to fall back on insulin. Basal insulin therapy is started first, which requires that the patient learn how to perform injections, self-monitor blood glucose levels, manage hypoglycaemia and perform dose titration. If glycaemic control is not attained, particularly due to lack of postprandial glycaemic control, an additional injection of a rapid-acting analogue may be prescribed before the meal most likely to provoke hyperglycaemia and then possibly before other meals.

Pre-mixed insulin may also be used, although it has the disadvantage of a slightly greater risk of hypoglycaemia and less flexibility for dose adjustment. In a study on 708 type 2 diabetic patients who were uncontrolled with metformin and sulfonylureas and had an HbA1c between 7% and 10%, the addition of biphasic insulin aspart two times daily, insulin aspart three times daily or insulin detemir once daily led to a similar improvement of the HbA1c at 1 year in the three groups (HbA1c at 1 year, respectively, 7.3%, 7.2% and 7.6%); weight gain and more frequent hypoglycaemia occurred in the biphasic aspart and the aspart versus detemir groups [15].

### 3.5. Other criteria may guide the treatment choice

In common practice, if the major objective is to avoid hypoglycaemia, pioglitazone (though no longer available in France) and incretin mimetics should be favoured. If one of the goals is to avoid weight gain, incretin mimetics are the most attractive
option. Finally, when taking into account care costs, sulfonylureas and insulin remain the least expensive drugs.

4. Future perspectives – Conclusion

New drugs will be added soon to those that are currently available and will quickly make this position statement obsolete. The new long-acting insulin analogues, the new GLP-1 analogues and the SGLT2 inhibitors (sodium-glucose co-transporter-2 inhibitors) will therefore provide additional tools for glycaemic regulation in diabetics [16,17].

While awaiting the French recommendations, the 2012 ADA-EASD consensus provides a remarkable road map by its simplicity and the possibilities it offers practitioners. The glycaemic and treatment objectives should be individualised, and patients should be involved in therapeutic decisions and goal setting. Multiple drug combinations are possible by taking into account each patient’s risk-benefit ratio. Further studies are of course necessary, particularly to identify factors that will predict treatment response.

It is nevertheless important to bear in mind that glycaemic management is part of cardiovascular risk reduction, which should be the main objective of the treatment. Glycaemic regulation should therefore necessarily be associated with combating other cardiovascular risk factors, as was well shown in the STENO 2 study where a 58% reduction in cardiovascular mortality was seen in the intensive group [18].

Finally, while studies reported at the ADA did not consider the different aspects of the ADA-EASD view, it should be noted that they support this consensus overall. This substantiates the interest in this text by the SFD, which took the initiative to translate it and make it available on its website.

Disclosure of interest

The authors have not supplied their declaration of conflict of interest.

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